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L26 ANSWER 1 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1999:547710 CAPLUS
DN 131:285340
TI I.kappa.B.alpha. gene transfer is cytotoxic to squamous-cell lung cancer cells and sensitizes them to tumor necrosis factor-.alpha.-mediated cell death
AU Batra, Raj K.; Guttridge, Denis C.; Brenner, David A.; Dubinett, Steven M.; Baldwin, Albert S.; Boucher, Richard C.
CS Department of Medicine and The Wadsworth Pulmonary Immunology Laboratory, West Los Angeles-Veterans Administration Medical Center/University of California Los Angeles, Los Angeles, CA, USA
SO Am. J. Respir. Cell Mol. Biol. (1999), 21(2), 238-245
CODEN: AJRBEL; ISSN: 1044-1549
PB American Lung Association
DT Journal
LA English
CC 15-10 (Immunochemistry)
AB Current paradigms in cancer therapy suggest that activation of nuclear factor-.kappa.B (NF-.kappa.B) by a variety of stimuli, including some cytoreductive agents, may **inhibit apoptosis**. Thus, inhibiting NF-.kappa.B activation may sensitize cells to anticancer therapy, thereby providing a more effective treatment for certain cancers.
E-1-deleted **adenoviral** (Ad) vectors encoding a "superrepressor" form of the NF-.kappa.B inhibitor I.kappa.B.alpha. (AdI.kappa.B.alpha.SR) or .beta.-galactosidase (AdLacZ) were tested alone and in combination with
tumor necrosis factor-.alpha. (TNF-.alpha.) in lung cancer cells for sensitization of the cells to death. Following transduction with AdI.kappa.B.alpha.SR, lung cancer cells expressed I.kappa.B.alpha.SR in a dose-dependent manner. Probing nuclear exts. of lung cancer cells with NF-.kappa.B-sequence-specific oligonucleotides indicated that there was a minimal amt. of NF-.kappa.B in the nucleus at baseline and an expected and
dramatic increase in nuclear NF-.kappa.B following exposure of cells to TNF-.alpha.. Control E-1-deleted AdLacZ did not promote NF-.kappa.B activation. Importantly, AdI.kappa.B.alpha.SR-mediated gene transfer resulted in the complete block of nuclear translocation of NF-.kappa.B by specific binding of its p65/relA component with transgenic I.kappa.B.alpha.SR. At the cellular level, transduction with AdI.kappa.B.alpha.SR resulted in increased cytotoxicity in lung cancer cells as opposed to transduction with equiv. doses of AdLacZ. In addn., whereas the parental cells were resistant to TNF-.alpha.-mediated cytotoxicity, I.kappa.B.alpha.SR-transduced cells could be sensitized to TNF-.alpha.. Consequently, AdI.kappa.B.alpha.SR transduction followed by exposure to TNF-.alpha. uniformly resulted in the death of non-small-cell lung cancer cells. These data suggest that novel approaches incorporating
I.kappa.B.alpha. **gene therapy** may have a role in the treatment of lung cancer.
ST IkappaBalpha gene transfer squamous cell lung cancer
IT Phosphoproteins
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(I.kappa.B-.alpha. (inhibitor of RNA formation factor NF-.kappa.B, .alpha.); I.kappa.B.alpha. gene transfer is cytotoxic to squamous-cell lung cancer cells and sensitizes them to tumor necrosis factor-.alpha.-mediated cell death)
IT Apoptosis
Squamous cell carcinoma (lung)

Transformation (genetic)
(I.kappa.B.alpha. gene transfer is cytotoxic to squamous-cell lung cancer cells and sensitizes them to tumor necrosis factor-.alpha.-mediated cell death)

IT Genes (animal)
Tumor necrosis factor .alpha.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(I.kappa.B.alpha. gene transfer is cytotoxic to squamous-cell lung cancer cells and sensitizes them to tumor necrosis factor-.alpha.-mediated cell death)

IT Cytotoxicity
Gene therapy
Lung tumor inhibitors
(I.kappa.B.alpha. gene transfer is cytotoxic to squamous-cell lung cancer cells and sensitizes them to tumor necrosis factor-.alpha.-mediated cell death in relation to)

IT NF-.kappa.B
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(I.kappa.B.alpha. gene transfer is cytotoxic to squamous-cell lung cancer cells and sensitizes them to tumor necrosis factor-.alpha.-mediated cell death in relation to)

L26 ANSWER 2 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1999:64907 CAPLUS
DN 130:135639
TI **Inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degradation) protein
IN Wold, William S. M.
PA Saint Louis University, USA
SO PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N007-01
ICS C12N015-34; C12N015-87
CC 6-3 (General Biochemistry)
Section cross-reference(s): 3
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9902658	A1	19990121	WO 1998-US14239	19980708
	W: AU, CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9882970	A1	19990208	AU 1998-82970	19980708
PRAI	US 1997-88993		19970709		
	WO 1998-US14239		19980708		

AB A method for **inhibiting apoptosis** of a cell expressing a death receptor of the tumor necrosis factor receptor (TNFR) family is disclosed. The method involves treating the cell with a Receptor Internalization and Degrdn. (RID) protein complex contg. RID.alpha. (10.4K) and RID.beta. (14.5K) proteins encoded by the E3 region of **adenovirus**. The RID complex reduces the no. of mols. of one or more death receptors (esp. Fas and TNFR-1) on the surface of the cell, resulting from internalization of the receptor to endosomes and degrdn. of the internalized death receptor by lysosomes. RID inhibits killing of **adenovirus**-infected cells by natural killer cells and cytotoxic lymphocytes. The cell can be treated by administering to the cell a polynucleotide expressing the RID complex or by administering to the cell a compn. contg. the RID complex. Compns. contg. a RID complex are also disclosed. Thus, a human **adenovirus** 5-derived vector (231-10) is constructed from which the E1 and E3 regions are deleted and contg. and expression cassette with the cytomegalovirus promoter controlling the E3

genes inserted into the deleted E1 region. This vector prevents rejection of human cancer cells transplanted into immunocompetent mice. The compns. and method are useful in the treatment of cancer, degenerative and immune disorders, as well as in promoting survival of tissue transplants.

ST protein RID receptor internalization degrdn **adenovirus**; apoptosis inhibition **adenovirus** protein RID; **gene therapy** apoptosis inhibition **adenovirus** protein RID

IT Cytokine receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(DR3, inhibition of apoptosis mediated by; **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT Proteins (specific proteins and subclasses)
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RID (receptor internalization and degrdn.); **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT Cytokine receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(TRAIL, inhibition of apoptosis mediated by; **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT Virus vectors
(**adenoviral** 231-10; **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT Apoptosis
Gene therapy
Human **adenovirus** 2
Human **adenovirus** 5
Leukocyte
Transplant (organ)
(**inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT Fas antigen
Tumor necrosis factor receptor p55
Tumor necrosis factor receptor p75
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of apoptosis mediated by; **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT DNA sequences
(of **adenovirus** 231-10 vector expressing RID (receptor internalization and degrdn.) protein complex components)

IT Protein sequences
(of **adenovirus** RID (receptor internalization and degrdn.) protein complex components)

IT Degenerative diseases
Immunodeficiency
(treatment of; **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT 95329-65-0, Protein (human **adenovirus** 5 early region E3B 14.5-kilodalton reduced) 126464-41-3, Protein (human **adenovirus** 2 early region E3 10.4-kilodalton precursor reduced) 219955-12-1
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

IT 220020-41-7P
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleotide sequence; **inhibiting apoptosis** with **adenovirus** RID (receptor internalization and degrdn.) protein)

L26 ANSWER 3 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1998:630357 CAPLUS
DN 130:247
TI Apoptosis by retrovirus- and **adenovirus**-mediated gene transfer of Fas ligand to glioma cells: implications for **gene therapy**
AU Shinoura, Nobusada; Yoshida, Yoko; Sadata, Akiko; Hanada, Ken-Ichi; Yamamoto, Shinji; Kirino, Takaaki; Asai, Akio; Hamada, Hirofumi
CS Department of Molecular Biotherapy Research, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo, 170-8455, Japan
SO Hum. Gene Ther. (1998), 9(14), 1983-1993
CODEN: HGTHE3; ISSN: 1043-0342
PB Mary Ann Liebert, Inc.
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 3
AB Astrocytic tumors frequently express Fas/APO-1 (Fas), in sharp contrast to surrounding normal brain cells, providing a potential window through which selective killing of tumor cells could be pursued. To assess this possibility, we transduced Fas into U251, a glioma cell line resistant to anti-Fas antibody-mediated apoptosis, and obtained transfectants with high levels of Fas expression. Anti-Fas antibody showed significantly enhanced cytotoxicity for the transfectants, suggesting that U251 cells maintained an intercellular cascade of Fas-mediated apoptosis. When U251 transfectants with high-level Fas expression were transduced with Fas ligand-encoding gene via retrovirus, they were unaffected by exposure to anti-Fas antibody or Fas ligand **adenovirus** (Adeno-FL). Thus, retroviral induction of Fas ligand into the glioma cells with high levels of Fas led to the selection of cells that were resistant to Fas-dependent apoptosis. These resistant U251 transfectants were susceptible to FADD **adenovirus** (Adeno-FADD)-induced apoptosis, indicating that a cascade of death signals was blocked at the steps between Fas ligand and FADD. As for **adenoviral** transduction of Fas ligand into gliomas, gliomas with a relatively high level of expression of Fas were remarkably sensitive to Adeno-FL-induced apoptosis. Besides, Adeno-FADD induced pronounced apoptosis in all glioma cells. Our data suggest the possibility of using **adenovirus**-mediated transduction of Fas ligand and FADD genes as a therapeutic approach to target gliomas.
ST glioma apoptosis **gene therapy** Fas ligand
IT Genes (microbial)
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(FADD; apoptosis by retrovirus- and **adenovirus**-mediated gene transfer of Fas ligand to glioma cells: implications for **gene therapy**)
IT Apoptosis
Gene therapy
Glioma **inhibitors**
Retroviridae
Transduction (genetic)
Virus vectors
(**apoptosis** by retrovirus- and **adenovirus**-mediated gene transfer of Fas ligand to glioma cells: implications for **gene therapy**)
IT Fas ligand
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(apoptosis by retrovirus- and **adenovirus**-mediated gene transfer of Fas ligand to glioma cells: implications for **gene therapy**)

L26 ANSWER 4 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1998:604997 CAPLUS
DN 129:184255
TI Apoptosis-inducing **gene therapy** of malignancies that lowers the ratio of Rb protein to apoptosis-inducing proteins ratio
IN Strauss, Michael; Sandig, Volker; Bartek, Jiri; Lukas, Jiri
PA Den.
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-12
ICS C07K014-47; C12N015-85; A61K048-00
CC 1-6 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9837190	A1	19980827	WO 1998-DK68	19980220
W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9859831	A1	19980909	AU 1998-59831	19980220

PRAI DK 1997-183 19970220
US 1997-919226 19970828
WO 1998-DK68 19980220

AB A method of inducing apoptosis by blocking cell division and lowering cellular concns. of the Rb protein is described. The lowering of abs. concns. of Rb protein is accompanied by an increase in the level of the p53 tumor suppressor protein brought about by expression of the p53 gene. **Gene therapy** of malignancies using expression cassettes for the p53 and an inhibitor cell division such as p16INK4 protein is described. Expression of the p16INK4 gene in HuH7 and LOVO cells using the cytomegalovirus immediate-early promoter induced expression of the endogenous gene leading to >40-fold increase in p16INK4 protein levels. This level of p16INK4 protein effectively blocked progression into S-phase with some cells entering apoptosis. Levels of Rb protein also dropped in these cells and the frequency of apoptosis increased dramatically when both genes were expressed in the same cell lines. Mice injected with HuH7 cells transformed with **adenovirus** expression vectors for p16INK4 and p53 proteins showed less frequent development of tumors (2 animals out of ten) and tumor vols. were very small (10% of those in control animals).

ST apoptosis induction tumor **gene therapy**; cell division inhibition tumor **gene therapy**; p53 apoptosis tumor **gene therapy**; MTS1 gene tumor **gene therapy**; p16INK4 tumor **gene therapy**

IT Human **adenovirus**
(Ad-p16-9 (recombinant), p16INK4 gene on; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Human **adenovirus**
(Ad-p53 (recombinant), p53 gene on; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Proteins (specific proteins and subclasses)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(Bak, gene for, in **gene therapy** of malignancies;
apoptosis-inducing **gene therapy** of malignancies
that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Apoptosis
Gene therapy
(apoptosis-inducing **gene therapy** of malignancies
that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Rb protein
p53 (protein)
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(apoptosis-inducing **gene therapy** of malignancies
that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Proteins (specific proteins and subclasses)
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(apoptosis-regulating; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Bax protein
Bcl-x protein
p15INK4B protein
p16INK4 protein
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gene for, in **gene therapy** of malignancies;
apoptosis-inducing **gene therapy** of malignancies
that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Breast tumors
Colorectal tumors
Kidney tumors
Liver tumors
Lung tumors
Melanoma
Pancreatic tumors
Prostatic tumors
Tumors (animal)
(**gene therapy** of; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Tumors (animal)
(head, **gene therapy** of; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Early promoter (genetic element)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immediate early, MTS1 and p53 gene expression from; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT p53 gene (animal)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in **gene therapy** of malignancies;
apoptosis-inducing **gene therapy** of malignancies
that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Genes (animal)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mts1, in **gene therapy** of malignancies;
apoptosis-inducing **gene therapy** of malignancies
that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Proteins (specific proteins and subclasses)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p18INK4, gene for, in **gene therapy** of malignancies; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Proteins (specific proteins and subclasses)

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p19INK4, gene for, in **gene therapy** of malignancies; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Proteins (specific proteins and subclasses)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p21KIP, gene for, in **gene therapy** of malignancies; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Proteins (specific proteins and subclasses)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p27KIP, gene for, in **gene therapy** of malignancies; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Proteins (specific proteins and subclasses)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p57KIP, gene for, in **gene therapy** of malignancies; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Cell division
(proteins **inhibiting**; **apoptosis**-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

IT Head
(tumors, **gene therapy** of; apoptosis-inducing **gene therapy** of malignancies that lowers ratio of Rb protein to apoptosis-inducing proteins ratio)

L26 ANSWER 5 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1998:168077 CAPLUS
DN 128:289832
TI Overexpression of Bcl-2 in bladder cancer cells **inhibits** **apoptosis** induced by cisplatin and **adenoviral**-mediated p53 gene transfer
AU Miyake, Hideaki; Hanada, Norihisa; Nakamura, Hideo; Kagawa, Shunsuke; Fujiwara, Toshiyoshi; Hara, Isao; Eto, Hiroshi; Gohji, Kazuo; Arakawa, Soichi; Kamidono, Sadao; Saya, Hideyuki
CS Department of Tumor Genetics and Biology, Kumamoto University School of Medicine, Kumamoto, 860, Japan
SO Oncogene (1998), 16(7), 933-943
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton Press
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 3
AB To investigate the effects of the expression of Bcl-2 protein in bladder cancer on the apoptosis induced by cisplatin or **adenoviral** -mediated p53 gene (Ad5CMV-p53) transfer, we transfected the bcl-2 gene into KoTCC-1, a human bladder cancer cell line that does not express the Bcl-2 protein. The Bcl-2-transfected KoTCC-1 (KoTCC-1/B) exhibited significantly higher resistance to both cisplatin and Ad5CMV-p53 transfer than did either the parental KoTCC-1 (KoTCC-1/P) or the vector-only transfected cell line (KoTCC-1/C). The flow cytometric anal. of the propidium iodide-stained nuclei and DNA fragmentation anal. after cisplatin or Ad5CMV-p53 treatment revealed DNA degrdn. in both KoTCC-1/P and KoTCC-1/C, whereas KoTCC1/B showed a marked inhibition of DNA degrdn. Following the treatment with cisplatin or Ad5CMV-p53, the accumulation of p53 protein was highly detectable for a long period in KoTCC-1/B compared to that in KoTTC-1/P and KoTCC-1/C. Furthermore, the cisplatin and Ad5CMV-p53 treatments each reduced the vol. of the s.c. tumors established in nude mice formed by KoTCC-1/P or KoTCC-1/C; in contrast, their reductive effects on the tumors formed by KoTCC-1/B were significantly suppressed. The i.p. tumor cell implantation model revealed that the

prognoses of mice injected with KoTCC-1/B were significantly inferior to those of the mice injected with either KoTCC-1/P or KoTCC-1/C after treatment with cisplatin or Ad5CMV-p53. These findings suggest that the expression of Bcl-2 in bladder cancer cells interferes with the therapeutic effects of cisplatin and Ad5CMV-p53 through the inhibition of the apoptotic pathway.

ST Bcl2 bladder cancer apoptosis cisplatin p53

IT Apoptosis
Bladder tumors
Drug resistance
Gene therapy
(overexpression of Bcl-2 in human bladder cancer cells **inhibits** **apoptosis** induced by cisplatin and **adenoviral** -mediated p53 gene transfer)

IT bcl-2 protein
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(overexpression of Bcl-2 in human bladder cancer cells **inhibits** **apoptosis** induced by cisplatin and **adenoviral** -mediated p53 gene transfer)

IT p53 gene (animal)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(overexpression of Bcl-2 in human bladder cancer cells **inhibits** **apoptosis** induced by cisplatin and **adenoviral** -mediated p53 gene transfer)

IT 15663-27-1, Cisplatin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(overexpression of Bcl-2 in human bladder cancer cells **inhibits** **apoptosis** induced by cisplatin and **adenoviral** -mediated p53 gene transfer)

L26 ANSWER 6 OF 6 CAPLUS COPYRIGHT 1999 ACS

AN 1996:263740 CAPLUS

DN 124:306811

TI bcl-xs **Gene therapy** induces apoptosis of human mammary tumors in nude mice

AU Ealovega, Mark W.; McGinnis, Patrick K.; Sumantran, Venil N.; Clarke, Michael F.; Wicha, Max S.

CS Department Internal Medicine, University Michigan Comprehensive Cancer Center, Ann Arbor, MI, 48109-0724, USA

SO Cancer Res. (1996), 56(9), 1965-9
CODEN: CNREA8; ISSN: 0008-5472

DT Journal

LA English

CC 1-6 (Pharmacology)
Section cross-reference(s): 3

AB Bel-xs is a dominant neg. repressor of Bel-2 and Bel-xL, both of which **inhibit apoptosis**. We used a replication-deficient **adenoviral** vector in transiently overexpress Bel-xs in MCF-7 human breast cancer cells, which overexpress Bel-xL. Infection with this vector induced apoptosis in vitro. We then detd. the effects of intratumoral injection of bel-xs **adenovirus** on solid MCF-7 tumors in nude mice. Tumors injected four times with the bel-xs **adenovirus** showed a 50% redn. in size. Using terminal transferase-mediated dUTP-digoxigenin nick end labeling, we obsd. apoptotic cells at sites of bel-xs **adenoviral** injection. These expts. demonstrate the feasibility of using bel-xs **gene therapy** to induce apoptosis in human breast tumors.

ST gene bclxs therapy mammary tumor apoptosis

IT Apoptosis
(bcl-xs **gene therapy** induces apoptosis of human mammary tumors in nude mice)

IT Gene, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bcl-xs; bcl-xs **gene therapy** induces apoptosis of human mammary tumors in nude mice)

IT Mammary gland
(neoplasm, bcl-xs **gene therapy** induces apoptosis of human mammary tumors in nude mice)

L34 ANSWER 4 OF 118 MEDLINE
AN 1998295829 MEDLINE
DN 98295829
TI Viral proteins that regulate cellular signalling.
AU Krajcsi P; **Wold W S**
CS Department of Medical Biochemistry, Semmelweis University of Medicine, Budapest, Hungary.. krajcsi@puskin.sote.hu
NC CA21470 (NCI)
CA58538 (NCI)
CA71704 (NCI)
SO JOURNAL OF GENERAL VIROLOGY, (1998 Jun) 79 (Pt 6) 1323-35. Ref: 180
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals; Cancer Journals
EM 199809
EW 19980902
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Death
Cell Division
*Signal Transduction
*Viral Proteins: PH, physiology
CN 0 (Vir

L34 ANSWER 5 OF 118 MEDLINE
AN 1998224706 MEDLINE
DN 98224706
TI Forced degradation of Fas inhibits apoptosis in adenovirus-infected cells.
AU Tollefson A E; Hermiston T W; Lichtenstein D L; Colle C F; Tripp R A; Dimitrov T; Toth K; Wells C E; Doherty P C; **Wold W S**
CS Department of Molecular Microbiology and Immunology, St Louis University School of Medicine, Missouri 63104-1004, USA.
SO NATURE, (1998 Apr 16) 392 (6677) 726-30.
Journal code: NSC. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199807
EW 19980703
AB DNA viruses have evolved elaborate mechanisms to overcome host antiviral defences. In adenovirus-infected cells, programmed cell death (apoptosis) induced by the cytokine tumour necrosis factor (TNF) is inhibited by several adenovirus-encoded proteins. Occupation of the cell-surface receptor Fas, a member of the TNF-receptor superfamily that is expressed on most cell types, triggers apoptosis of that cell. Here we show that the adenovirus RID (for receptor internalization and degradation) protein complex, which is an inhibitor of TNF-induced apoptosis, mediates internalization of cell-surface Fas and its destruction inside lysosomes within the cell. Fas has not previously been shown to be internalized and then degraded. RID also mediates internalization of the receptor for epidermal growth factor, but it does not affect the transferrin receptor or class I antigens of the major histocompatibility complex. Removal of Fas from the surface of adenovirus-infected cells expressing RID may allow infected cells to resist Fas-mediated cell death and thus promote their survival.
CT Check Tags: Animal; Human
*Adenoviridae: PH, physiology
Adenovirus E1B Proteins
Antibiotics, Macrolide: PD, pharmacology
*Antigens, CD95: PH, physiology
*Apoptosis
Cell Line, Transformed
Mice
Mutation
Viral Proteins
RN 88899-55-2 (bafilomycin A1)
CN 0 (Adenovirus E1B Proteins); 0 (Antibiotics, Macrolide); 0 (Antigens, CD95)

L34 ANSWER 6 OF 118 MEDLINE
AN 97213949 MEDLINE
DN 97213949
TI Adenovirus E3-10.4K/14.5K protein complex inhibits tumor necrosis factor-induced translocation of cytosolic phospholipase A2 to membranes.
AU Dimitrov T; Krajcsi P; Hermiston T W; Tollefson A E; Hannink M; **Wold W S**
CS Department of Molecular Microbiology and Immunology, St. Louis University School of Medicine, Missouri 63104, USA.
NC CA58538 (NCI)
CA24710 (NCI)
SO JOURNAL OF VIROLOGY, (1997 Apr) 71 (4) 2830-7.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199706
EW 19970603
AB We have reported that three adenovirus (Ad) proteins, named E3-10.4K/14.5K, E3-14.7K, and E1B-19K, independently inhibit tumor necrosis factor (TNF)-induced apoptosis in Ad-infected cells. E3-10.4K/14.5K and E3-14.7K also inhibit TNF-induced release of arachidonic acid (AA). TNF-induced apoptosis and AA release are thought to require TNF-activation of the 85-kDa cytosolic phospholipase A2 (cPLA2). cPLA2 normally exists in a latent form in the cytosol; it is activated by phosphorylation by mitogen-activated protein kinase, and in the presence of agents that mobilize intracellular Ca2+, cPLA2 translocates to membranes where it cleaves AA from membrane phospholipids. We now report that TNF induces translocation of cPLA2 from the cytosol to membranes in Ad-infected human A549 cells and that E3-10.4K/14.5K but not E3-14.7K or E1B-19K is required to inhibit TNF-induced translocation of cPLA2. Ad infection also inhibited TNF-induced release of AA. Under the same conditions, Ad infection did not inhibit TNF-induced phosphorylation of cPLA2 or TNF activation of NFkappaB. Ad infection also inhibited cPLA2 translocation in response to the Ca2+ ionophore A23187 and to cycloheximide, but this inhibition did not require E3-10.4K/14.5K. Ad infection did not inhibit cPLA2 translocation in response to interleukin-1beta or platelet-derived growth factor. We propose that E3-10.4K/14.5K inhibits TNF-induced AA release and apoptosis by directly or indirectly inhibiting TNF-induced translocation of cPLA2 from the cytosol to membranes. AA formed by cPLA2 can be metabolized to prostaglandins, leukotrienes, and lipoxyns, molecules that amplify inflammation. E3-10.4K/14.5K probably functions in Ad infections to inhibit both TNF-induced apoptosis and inflammation.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Adenovirus E3 Proteins: ME, metabolism
*Adenoviruses, Human: ME, metabolism
Apoptosis
Biological Transport
Cell Membrane: ME, metabolism
Cytosol: ME, metabolism
NF-kappa B: GE, genetics
NF-kappa B: ME, metabolism
*Phospholipases A: ME, metabolism
Tumor Cells, Cultured
Tumor Necrosis Factor: AI, antagonists & inhibitors
*Tumor Necrosis Factor: PD, pharmacology
CN EC 3.1.1.- (Phospholipases A); 0 (Adenovirus E3 Proteins); 0 (NF-kappa B);

0 (Tumor Necrosis Factor)

L34 ANSWER 7 OF 118 MEDLINE

AN 96357009 MEDLINE

DN 96357009

TI The adenovirus E3-14.7K protein and the E3-10.4K/14.5K complex of proteins, which independently inhibit tumor necrosis factor (TNF)-induced apoptosis, also independently inhibit TNF-induced release of arachidonic acid.

AU Krajcsi P; Dimitrov T; Hermiston T W; Tollefson A E; Ranheim T S; Vande Pol S B; Stephenson A H; **Wold W S**

CS Department of Molecular Microbiology and Immunology, St. Louis University Schoolof Medicine, Missouri 63104, USA.

SO JOURNAL OF VIROLOGY, (1996 Aug) 70 (8) 4904-13.
Journal code: KCV. ISSN: 0022-538X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199701

EW 19970104

AB Tumor necrosis factor (TNF) is an inflammatory cytokine that inhibits the replication of many viruses in cultured cells. We have reported that adenovirus (Ad) infection of TNF-resistant mouse cells renders them susceptible to lysis by TNF and that two sets of proteins encoded by the E3 transcription unit block TNF cytolysis. The E3 protein sets are named E3-14.7K (14,700 kDa) and E3-10.4K/14.5K (a complex of two proteins of 10,400 and 14,500 kDa). TNF activation of the 85-kDa cytosolic phospholipase A2 (cPLA2) is thought to be essential for TNF cytolysis (i.e.,TNF-induced apoptosis). Here we provide evidence that cPLA2 is important in the response of Ad-infected cells to TNF and that the mechanism by which E3-14.7K and E3-10.4K/14.5K inhibit TNF cytolysis is by inhibiting TNF activation of cPLA2. cPLA2 cleaves arachidonic acid (AA) specifically from membrane phospholipids; therefore, cPLA2 activity was measured by the release of 3H-AA from cells prelabeled with 3H-AA. Uninfected cells or cells infected with wild-type Ad were not lysed and did not release 3H-AA in response to TNF. In contrast, TNF treatment induced cytolysis and 3H-AA release in uninfected cells sensitized to TNF by treatment with cycloheximide and also in infected cells sensitized to TNF by expression of E1A. In C127 cells, in which either E3-14.7K or E3-10.4K/14.5K inhibits TNF cytolysis, either set of proteins inhibited TNF-induced release of 3H-AA. In C3HA cells, in which E3-14.7K but not E3-10.4K/14.5K prevents TNF cytolysis, E3-14.7K but not E3-10.4K/14.5K prevented TNF-induced release of 3H-AA. When five virus mutants with lesions in E3-14.7K were examined, there was a perfect correlation between a mutant's ability to inhibit both TNF-induced cytolysis and release of 3H-AA. E3-14.7K expressed in two stably transfected C127 cell lines prevented both TNF-cycloheximide-induced cytolysis and release of 3H-AA. The E3 proteins also prevented TNF-induced cytolysis and release of 3H-AA in mouse L929 cells, which are spontaneously sensitive to TNF. TNF cytolysis was blocked by dexamethasone, an inhibitor of PLA2 activity, and by nordihydroquaiaretic acid, which inhibits the metabolism of AA to the leukotrienes. Indomethacin, which blocks the formation of prostaglandins from AA, did not inhibit TNF cytolysis. The leukotrienes and prostaglandins are amplifiers of the inflammatory response. We propose that E3-14.7K and E3-10.4K/14.5K function independently in Ad infection to inhibit both cytolysis and inflammation induced by TNF.

CT Check Tags: Animal

*Adenoviridae Infections
Adenoviridae Infections: ME, metabolism
Adenoviridae Infections: PA, pathology
*Adenovirus E3 Proteins: PD, pharmacology
*Apoptosis: DE, drug effects
*Arachidonic Acid: ME, metabolism
Cell Line
Mice
Phospholipases A: AI, antagonists & inhibitors
*Tumor Necrosis Factor: AI, antagonists & inhibitors
Tumor Necrosis Factor: PD, pharmacology
RN 506-32-1 (Arachidonic Acid)
CN EC 3.1.1.- (Phospholipases A); 0 (Adenovirus E3 Proteins); 0 (Tumor Necro

L34 ANSWER 9 OF 118 MEDLINE
AN 96183890 MEDLINE
DN 96183890
TI The role of human adenovirus early region 3 proteins (gp19K, 10.4K, 14.5K,
and 14.7K) in a murine pneumonia model.
AU Sparer T E; Tripp R A; Dillehay D L; Hermiston T W; **Wold W S**; Gooding L R
CS Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
NC CA58736 (NCI)
CA24710 (NCI)
CA58538 (NCI)
SO JOURNAL OF VIROLOGY, (1996 Apr) 70 (4) 2431-9.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199609
AB Products of human adenovirus (Ad) early region 3 (E3) inhibit both specific (cytotoxic T lymphocytes [CTLs]) and innate (tumor necrosis factor alpha [TNF-alpha]) immune responses in vitro. The E3 gp19K protein prevents CTL recognition of Ad-infected fibroblasts by sequestering major histocompatibility complex class I proteins in the endoplasmic reticulum. E3 proteins 10.4K, 14.5K, and 14.7K function to protect infected cells from TNF-alpha cytolysis. To address the in vivo functions of these proteins, Ad mutants that lack the E3 genes encoding these proteins were inoculated intranasally into C57BL/10SnJ (H-2b) mice. Mutants that lack the gp19K gene failed to alter CTL generation or to affect Ad-induced pulmonary infiltrates. Since gamma interferon (IFN-gamma) is capable of overcoming gp19K suppression of CTL lysis in vitro, mice were depleted of IFN-gamma and inoculated with gp19K mutants. Even when IFN-gamma was depleted, gp19K was incapable of altering pulmonary lesions. These resuls are not in accord with the function of gp19K in vitro and suggest that gp19K does not affect immune recognition in vivo during an acute virus infection, yet they do not exclude the possibility that gp19K blocks immune recognition of Ad during a persistent infection. In contrast, when mice were inoculated with Ad mutants that lack the TNF resistance genes (14.7K and either 10.4K or 14.5K), there was a marked increase in alveolar
infiltration and no change in the amounts of perivascular/peribronchiolar infiltration compared with wild-type-Ad-induced pathology. These findings demonstrate the importance of TNF susceptibility and TNF by-products for recruiting inflammatory cells into the lungs during Ad infections.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenoviridae Infections: IM, immunology
Adenoviridae Infections: PA, pathology
*Adenoviridae Infections: VI, virology
Adenovirus E3 Proteins: IM, immunology
*Adenovirus E3 Proteins: PH, physiology
Adenoviruses, Human: IM, immunology
*Adenoviruses, Human: PH, physiology
Cell Line, Transformed
Immunity, Natural: IM, immunology
Interferon Type II: IM, immunology
Mice
Mice, Inbred C57BL
Pneumonia, Viral: IM, immunology

Pneumonia, Viral: PA, pathology
*Pneumonia, Viral: VI, virology
T-Lymphocytes, Cytotoxic: IM, immunology
Tumor Necrosis Factor: IM, immunology
RN 82115-62-6 (Interferon Type II)
CN 0 (Adenovirus E3 Proteins); 0 (Tumor Necrosis Factor)

L34 ANSWER 12 OF 118 MEDLINE
AN 96030039 MEDLINE
DN 96030039
TI Tumor necrosis factor alpha increases expression of adenovirus E3 proteins.
AU Deryckere F; Ebenau-Jehle C; **Wold W S**; Burgert H G
CS Spemann Laboratories, Max-Planck-Institute for Immunobiology, Freiburg, Germany.
SO IMMUNOBIOLOGY, (1995 Jul) 193 (2-4) 186-92. Ref: 16
Journal code: GH3. ISSN: 0171-2985.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199604
AB Human adenovirus can cause persistent infections in man. Implicated in this phenomenon is the early transcription unit 3 (E3) of the virus which encodes proteins that are primarily devoted to counteract the lytic attack by the host immune system: Several E3 proteins (14.7K, 10.4K and 14.5K) protect infected cells from the lytic activity of tumor necrosis factor alpha (TNF) while the most abundant E3 protein, E3/19K, inhibits lysis by cytotoxic T cells. E3/19K interacts with class I histocompatibility (MHC) antigens in the rough endoplasmic reticulum, thereby preventing transport of MHC molecules to the cell surface and, consequently, MHC-restricted T cell recognition. In addition, the 10.4K and 14.5K proteins downregulate cell surface expression of the epidermal growth factor receptor. Interestingly, adenovirus-mediated pneumonia in mice is accompanied by induction of TNF, a cytokine known to enhance MHC expression. We previously showed that TNF is unable to restore MHC class I expression in E3/19K transfected cells but rather leads to a further reduction of MHC antigens. This effect correlated with an increased production of E3/19K mRNA and protein. We now find in addition an upregulation of other E3 proteins in transfected as well as in infected cells. This coordinated upregulation of E3 proteins indicates that TNF stimulates the E3 promoter, probably by activating the transcription factor NF-kappa B. Thus, a novel interaction between the immune system and adenovirus is described in which the virus takes advantage of an immune mediator to promote expression of several immunosubversive proteins supporting its escape from immunosurveillance.
CT Check Tags: Animal; Human
*Adenovirus E3 Proteins: BI, biosynthesis
*Adenovirus E3 Proteins: DE, drug effects
*Tumor Necrosis Factor: PH, physiology
Up-Regulation (Physiology): IM, immunology
CN 0 (Adenovirus E3 Proteins); 0 (Tumor Necrosis Factor)

L34 ANSWER 13 OF 118 MEDLINE
AN 96004190 MEDLINE
DN 96004190
TI E3 transcription unit of adenovirus.
AU **Wold W S**; Tollefson A E; Hermiston T W
CS Department of Molecular Microbiology and Immunology, St. Louis University School of Medicine, MO 63104, USA..
NC CA24710 (NCI)
CA58538 (NCI)

CA49540 (NCI)
SO CURRENT TOPICS IN MICROBIOLOGY AND IMMUNOLOGY, (1995) 199 (Pt 1) 237-74.
Ref: 196
Journal code: DWQ. ISSN: 0070-217X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
EM 199601
CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
Adenovirus E3 Proteins: CH, chemistry
*Adenovirus E3 Proteins: GE, genetics
Adenovirus E3 Proteins: ME, metabolism
*Adenoviruses, Human: GE, genetics
Adenoviruses, Human: IM, immunology
Amino Acid Sequence
Base Sequence
Molecular Sequence Data
RNA, Viral
*Transcription, Genetic
CN 0 (Adenovirus E3 Proteins); 0 (RNA, Viral)

L34 ANSWER 18 OF 118 MEDLINE
AN 95074862 MEDLINE
DN 95074862
TI The adenovirus E3 10.4K and 14.5K proteins, which function to prevent cytolysis by tumor necrosis factor and to down-regulate the epidermal growth factor receptor, are localized in the plasma membrane.
AU Stewart A R; Tollefson A E; Krajcsi P; Yei S P; **Wold W S**
CS Department of Molecular Microbiology and Immunology, St. Louis University School of Medicine, Missouri 63104..
NC CA58538 (NCI)
CA24710 (NCI)
CA49540 (NCI)
SO JOURNAL OF VIROLOGY, (1995 Jan) 69 (1) 172-81.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199503
AB The adenovirus type 2 and 5 E3 10,400- and 14,500-molecular-weight (10.4K and 14.5K) proteins are both required to protect some cell lines from lysis by tumor necrosis factor and to down-regulate the epidermal growth factor receptor. We have shown previously that both 10.4K and 14.5K are integral membrane proteins and that 14.5K is phosphorylated and O glycosylated. The 10.4K protein coimmunoprecipitates with 14.5K, indicating that the two proteins function as a complex. Here we show, using immunofluorescence and two different cell surface-labeling techniques, that both proteins are localized in the plasma membrane. In addition, we show that trafficking of each protein to the plasma membrane depends on concomitant expression of the other protein. Finally, neither protein could be immunoprecipitated from conditioned media, indicating that neither is secreted. Taken together, these results suggest that the plasma membrane is the site at which 10.4K and 14.5K function to inhibit cytolysis by tumor necrosis factor and to down-regulate the epidermal growth factor receptor.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Adenovirus E3 Proteins: PH, physiology
Amino Acid Sequence
Cell Death
Cells, Cultured
Down-Regulation (Physiology)
*Membrane Proteins: PH, physiology
Molecular Sequence Data
Protein Processing, Post-Translational
*Receptors, Epidermal Growth Factor-Urogastrone: ME, metabolism
Subcellular Fractions: ME, metabolism
*Tumor Necrosis Factor: AI, antagonists & inhibitors
CN 0 (Adenovirus E3 Proteins); 0 (Membrane Proteins); 0 (Receptors, Epidermal
Growth Factor-Urogastrone); 0 (Tumor Necrosis Factor)